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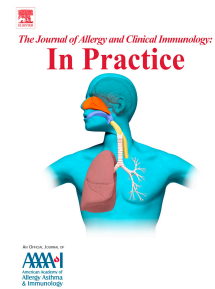
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Consistently Very Poorly Controlled Asthma is Associated with Greater Activity and School Impairment in Children with Severe or Difficult-to-Treat Asthma

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Conflict of interest

L.B. Bacharier is a consultant/speaker bureau for Novartis; reports grants from NIH, and personal fees from Aerocrine, GlaxoSmithKline, Merck, DBV Technologies, Teva, Boehringer Ingelheim, AstraZeneca, WebMD/Medscape, Sanofi/Regeneron, Vectura, and Circassia. R.A. Covar is a consultant/advisory board member for Genentech, Inc., Novartis, and GSK; and has participated as a study investigator for NHLBI, GSK, Astra Zeneca, and Roche. T. Haselkorn is a consultant for Genentech, Inc. and Novartis Pharmaceuticals Corp. A. Iqbal and H. Chen are employees of Genentech, Inc. C. Alvarez and D.R. Mink received funding from Genentech, Inc. through their employer, ICON Clinical Research, for statistical support of the TENOR study. R.S. Zeiger received grant funding/research support to Kaiser Permanente from Genentech, Inc. and also Aerocrine, AstraZeneca, GlaxoSmithKline, MERCK and Co, and NHLBI; is a consultant/advisory board member for Genentech, Inc., Novartis, AstraZeneca, GlaxoSmithKline, Merck & Co, Inc., MedImmune, Patara Pharma, Regeneron Pharmaceuticals, Sanofi, TEVA Pharmaceutical Industries, and Theravance BioPharma.

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Previous presentation of data

These data were previously presented at the American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting, March 3-6, 2017, Atlanta, Georgia, and the Pediatric Academic Societies 2017 Annual Meeting, May 6-9, 2017, San Francisco, California.

Clinical Implications: Children aged 6-11 years with consistently very poorly controlled asthma, as defined by the NHLBI asthma guidelines, had greater activity and overall school impairment, and school absences than children whose asthma improved over time.

TO THE EDITOR:

Asthma that is not well controlled contributes to school absences and/or affects performance while in school.¹⁻³ In 2013, children with asthma experienced 13.8 million missed school days,⁵ and between 2008 to 2013, there was an estimated national loss of 1.1 billion dollars from school absenteeism attributed to asthma.⁴ Studies have reported an association between scores on the Work Productivity and Activity Impairment questionnaire specific to asthma (WPAI:Asthma) and other patient-reported outcomes and predicted healthcare utilization in adolescent and adult patients.⁶ Severe asthma in children is a complicated and heterogeneous disorder that is challenging to treat, with a small, but significant subset of children who require higher intensity therapy to maintain symptoms control, or who may remain uncontrolled despite such therapy.^{7,8} Activity and overall school impairment in school-age children with severe or difficult-to-treat asthma has not been reported. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study provides a unique opportunity to evaluate the relationship between the impairment domain of the National Heart, Lung, and Blood Institute (NHLBI) guidelines and school and activity impairment in children. The present analysis examines longitudinal activity impairment, overall school impairment, and missed school days in children with consistently very poorly controlled (VPC) asthma compared with children

whose asthma improved from VPC. We hypothesized that VPC disease in children with severe or difficult-to-treat asthma would be associated with activity and school impairment.

TENOR was a 3-year (2001-2004), multicenter, observational study of patients 6 years of age and older with severe or difficult-to-treat asthma. This analysis included children 6-11 years of age at baseline, with data representing the impairment domain of the Expert Panel Report 3 asthma guidelines¹ and responses to the WPAI:Asthma.⁶ The WPAI:Asthma assessed activity and school impairment in the 7 days before completion at baseline, Month 12, and Month 24. Scoring ranged from 0-100%, with higher scores indicating greater impairment. Two main subgroups were analyzed based on the impairment domain of the NHLBI guidelines. The first subgroup, termed “consistently VPC”, included children with VPC asthma at baseline and VPC asthma throughout the 2 years of follow-up (Month 12 and Month 24). The second subgroup, termed “improved from VPC”, included children with VPC asthma at baseline who exhibited improvement in asthma control by becoming either well-controlled and/or not well-controlled (but not VPC) at Month 12 and Month 24.

A total of 51 children were identified as having consistently VPC asthma, while a total of 31 children were identified as having improved from VPC asthma. Baseline characteristics for each subgroup are summarized in **Table 1**. Compared to children whose VPC improved, the consistently VPC asthma subgroup exhibited the following significant differences: (1) a higher proportion of Black children (35.3% vs. 9.7%, $P<0.05$ for overall comparison of race/ethnicity), (2) a lower proportion of privately insured (60.8% vs. 83.9%, $P<0.05$), (3) a higher frequency of use of 3 or more controller medications (78.4% vs. 54.8%, $P<0.01$), and (4) a higher prevalence of a history of atopic dermatitis (19.6% vs. 0.0%, $p<0.05$).

Activity impairment, overall school impairment, and number of hours per week missed in school are summarized in **Figure 1**. When assessing activity impairment, children who had consistently VPC asthma exhibited significantly greater indicators of asthma-related impairment than children who had improved from having VPC asthma at both Month 12 and Month 24 (Month 12 scores: 30.2 vs. 10.3, $P = 0.002$. Month 24 scores: 31.1 vs. 9.3, $P < 0.001$, respectively). Similarly, when examining overall school impairment, children who were consistently VPC were significantly more impaired than children who had improved from having VPC asthma at both Month 12 and Month 24 (Month 12 scores: 30.4 vs. 6.5, $P = 0.005$. Month 24 scores: 24.9 vs. 5.2, $P = 0.002$, respectively). While the number of hours per week missed in school were similar for both groups at baseline and Month 12, they were significantly different at Month 24, with an average of 3 hours missed per week for children who were consistently VPC and 0 hours missed per week for children who had improved from having VPC asthma ($P = 0.033$).

Limitations should be considered when interpreting these results. First, sampling bias may be introduced due to the small subgroup sizes in the analysis. Second, the results represent specialist care between 2001 and 2004 in the United States and may not be generalizable to asthma in primary care practice or in present day care, although this seems unlikely given the ongoing high rates of uncontrolled asthma.^{7,9}

The TENOR 3-year observational study provided an opportunity to examine the longitudinal impact of having consistently VPC asthma on school and activity impairment in children with severe or difficult-to-treat asthma. Compared with children whose asthma control improved from VPC, children with consistently VPC asthma had significantly greater activity and school impairment and a greater number of missed school hours. These results highlight the impact of asthma control on activity and school impairment and suggest that

118 improvement in asthma control may decrease activity and school impairment in these
119 children. These findings shed light on the need for improved asthma management strategies
120 to minimize asthma-related school absenteeism and activity limitation. As a substantial
121 number of school-age children receiving specialist care continue to have poor asthma
122 control despite the prescription of multiple controller medications, with consequent
123 adverse impact on activity and school performance, strategies are needed to address the
124 challenges of optimizing the use of these current interventions, including medication burden
125 and nonadherence to prescribed treatments.

REFERENCES

1. National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. Expert Panel Report 3: guidelines for the diagnosis and management of asthma, 2007.
www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
Accessed February 21, 2018.
2. Stridsman C, Dahlberg E, Zandén K, Hedman L. Asthma in adolescence affects daily life and school attendance – Two cross-sectional population-based studies 10 years apart. *Nursing Open*. 2017;4(3):143-148. doi:10.1002/nop2.77.
3. Hsu J., Qin X., Beavers S.F., Mirabelli M.C. Asthma-Related School Absenteeism, Morbidity, and Modifiable Factors. *Am J Prev Med* 2016;51(1):23–32.
4. Nurmagambetov T., Kuwahara R., Garbe P. The Economic Burden of Asthma in the United States, 2008–2013. *Ann Am Thorac Soc*. 2018;15(3):348-356.
5. Centers for Disease Control and Prevention. AsthmaStats. Asthma-related missed school days among children aged 5–17 years.
www.cdc.gov/asthma/asthma_stats/AstStatChild_Missed_School_Days.pdf.
Accessed February 21, 2018.
6. Chen H., Blanc P.D., Hayden M.L., Bleecker E.R., Chawla A., Lee J.H.; TENOR Study Group. *Value in Health*. 2008;11(2):231–239.
7. Fitzpatrick AM. Severe asthma in children: Lessons learned and future directions. *J Allergy Clin Immunol Pract* 2016;4(1):11-19.
8. Ramratnam SK, Bacharier LBB, Guilbert TW. Severe asthma in children. *J Allergy Clin Immunol Pract* 2017;5(4):889-898.

- 149 9. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet L-P.
150 Global asthma prevalence in adults: findings from the cross-sectional world
151 health survey. BMC Public Health 2012;12:204.

Table I. Baseline Characteristics of Children 6–11 Years of Age in TENOR with Consistently VPC or Improved From VPC Asthma

Characteristic	Consistently VPC Asthma (N=51)	Improved from VPC Asthma (N=31)	Between - Group Difference	95% CI for Between - Group Difference	P Value ^a
Mean±SD age at baseline, y	8.8±1.7	9.2±1.8	−0.4	−1.2, 0.4	NS
Female, n (%)	15 (29.4)	11 (35.5)	−6.1	−27.1, 14.9	NS
Race/ethnicity, n (%) ^b					<0.05
White	24 (47.1)	23 (74.2)	−27.1	−47.8, −6.5	
Black	18 (35.3)	3 (9.7)	25.6	8.9, 42.4	
Other	9 (17.6)	5 (16.1)	1.5	−15.1, 18.2	
Insurance status, n (%)					<0.05
Private insurance	31 (60.8)	26 (83.9)	−23.1	−41.7, −4.5	
Nonprivate insurance	20 (39.2)	5 (16.1)	23.1	4.5, 41.7	
BMI categories, n (%)					NS
≥95%	19 (37.3)	7 (22.6)	14.7	−5.1, 34.5	
85% to <95%	5 (9.8)	8 (25.8)	−16.0	−33.4, 1.4	
0% to <85%	27 (52.9)	16 (51.6)	1.3	−21.0, 23.6	
Mean±SD duration of asthma	6.4±2.3	5.5±2.9	0.9	−0.2, 2.1	NS
Geometric mean (95% CI) IgE, IU/mL	253.6 (156.0–	199.9 (106.8–	1.3 ^c	0.6, 2.8 ^d	NS
No. of controllers, n (%) ^b					<0.01
1	0	4 (12.9)	−12.9	−24.7, −1.1	
2	11 (21.6)	10 (32.3)	−10.7	−30.6, 9.3	
≥3	40 (78.4)	17 (54.8)	23.6	2.8, 44.4	
Mean±SD race-adjusted % predicted prebronchodilator	84.1±25.1	88.3±10.4	−4.2	−14.5, 6.2	NS
Mean±SD race-adjusted % predicted postbronchodilator	94.1±23.4	94.5±10.7	−0.5	−10.2, 9.3	NS
History of atopic dermatitis, n	10 (19.6)	0	19.6	8.7, 30.5	<0.05
History of allergic rhinitis, n	27 (52.9)	19 (61.3)	−8.4	−30.3, 13.6	NS
Children with ≥1 allergic asthma trigger(s), n (%) ^e	41 (80.4)	26 (83.9)	−3.5	−20.4, 13.4	NS
Children with ≥1 nonallergic asthma trigger(s), n (%) ^{b,f}	46 (90.2)	28 (90.3)	−0.1	−13.4, 13.1	NS
History of skin test positivity, n (%) ^b	28 (54.9)	10 (32.3)	22.6	1.3, 44.0	NS

NS, not significant; BMI, body mass index; FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E;

VPC, very poorly controlled. ^aFor between-group difference. ^bFisher's exact test used due to small cell size.

^cRatio. ^d95% CI for ratio. ^eAllergic triggers include pollen, animals, mold and/or dampness, and dust. ^fNonallergic

triggers include emotional stress and cold and/or sinus infection.

158 **Figure 1.** WPAI:Asthma **(A)** Activity Impairment, **(B)** School Impairment, and **(C)** Missed
159 School Hours/Week. VPC, very poorly controlled, WPAI, Work Productivity and Activity
160 Impairment, * $P<0.001$, † $P<0.01$, ‡ $P<0.05$

161

1 **Figure 1.** WPAI:Asthma (A) Activity Impairment, (B) School Impairment, and (C) Missed
2 School Hours/Week. VPC, very poorly controlled, WPAI, Work Productivity and Activity
3 Impairment, * $P<0.001$, † $P<0.01$, ‡ $P<0.05$

